UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/964,042	09/26/2001	Ralph Weichselbaum	27373/36638A	1056

4743 7590 02/24/2006

MARSHALL, GERSTEIN & BORUN LLP
233 S. WACKER DRIVE, SUITE 6300
SEARS TOWER
CHICAGO, IL 60606

EXAMINER	
ANGELL, JON E	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 02/24/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/964,042	WEICHSELBAUM ET AL.	
	Examiner	Art Unit	
	Jon Eric Angell	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 November 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14 and 16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14 and 16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11/28/2005 has been entered.

Claims 1-14 and 16 are currently pending in the application and are addressed herein.

Specification

The specification remains objected to as previously indicated because the amendment filed 11/18/2004 because it introduces new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: the 46 genes that are dispensable for viral replication that applicants have added to the paragraph beginning on page 4, lines 26 of the specification.

Applicants assert that the amendment is not new matter because the specification indicates that the Roizman articles (PNAS 1996) has been incorporated by reference (See page 5 of the communication received on 11/18/2004).

Applicants are respectfully reminded that MPEP § 608.01(p) indicates:

> "An application as filed must be complete in itself in order to comply with 35 U.S.C. 112. Material nevertheless may be incorporated by reference, *Ex parte Schwarze*, 151 USPQ 426 (Bd. Ape. 1966). An application for a patent when filed may incorporate 'essential material' by reference to (1) a U.S. patent, (2) a U.S. patent application publication, or (3)

> a pending U.S. application, subject to the conditions set forth below. 'Essential material' is defined as that which is necessary to (1) describe the claimed invention, (2) provide an enabling disclosure of the claimed invention, or (3) describe the best mode (35 U.S.C. 112). In any application which is to issue as a U.S. patent, essential material may not be incorporated by reference to (1) patents or applications published by foreign countries or a regional patent office, **(2) non-patent publications**, (3) a U.S. patent or application which itself incorporates 'essential material' by reference, or (4) a foreign application. Nonessential subject matter may be incorporated by reference to (1) patents or applications published by the United States or foreign countries or regional patent offices, (2) prior filed, commonly owned U.S. applications, or (3) non-patent publications however, aperients and/or other forms of browser executable code cannot be incorporated by reference. See MPEP § 608.01. Nonessential subject matter is subject matter referred to for purposes of indicating the background of the invention or illustrating the state of the art."

In the instant case, the material which has been added to the specification is considered "essential material" because it is necessary to describe the claimed invention. It is noted that claim 5 comprises the specific essential material that has been added to the specification. Since the new material added to the specification is "essential material" it may not be incorporated by reference to a non-patent publication as indicated above (See MPEP § 608.01(p)). Therefore, the new material is new matter.

Applicant is required to cancel the new matter in the reply to this Office Action.

Claim Rejections - 35 USC § 112, 1st paragraph

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1-5 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant

art that the inventor(s), at the time the application was filed, had possession of the claimed invention for the reasons of record (see the Office Action mailed on 6/15/2004), which are reiterated below for convenience. **This is a new matter rejection.**

3. Claim 5 is drawn to the method of claim 1, 2, 3, or 4 wherein the modified HSV genome further comprises deletion of a gene selected from a large group (see claim 5). However, looking to the specification for support, it is clear that claim 5 encompasses genes that were not disclosed in the originally filed specification. Specifically, the Examiner can only find support in the originally filed specification for the following genes: UL16, UL24, UL40, UL41, UL55, UL56, alpha22, US4, US8 and US11. Support cannot be found for the other genes. The Applicants are asked to specifically identify where, by page and line number, support for the other genes can be found.

4. Claims 1-14 and 16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

> A method for reducing tumor mass by directly injecting an HSV that expresses only one gamma(1)34.5 gene product into a tumor in an amount effective to reduce the mass of said tumor;

does not reasonably provide enablement for treatment in an individual via any route of administration other than direct injection. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make/use the invention commensurate in scope with these claims.

The following factors have been determined by the courts to be critical in determining whether a claimed invention is enabled (See In re Wands 8 USPQ 2d 1400, Fed. Cir. 1988).

The nature of the invention: The instant claims are drawn to a method for reducing tumor mass in an "individual" comprising administering an amount of recombinant Herpes simplex virus (HSV) wherein said HSV genome comprises a modification of an inverted repeat region such that one $\gamma_1$34.5 gene remains intact and where in said amount of HSV is being effective to reduce tumor mass. Thus, the nature of the invention is a therapeutic use of attenuated HSV virus for treating tumors and generally falls in the realm of oncolytic virotherapy. It is acknowledged that the instant claims are not drawn to methods of gene therapy. However, the oncolytic virotherapy does require that the therapeutic nucleic acid be delivered specifically to the desired cells, in this case the tumor cells. As such, an evaluation of delivery of the therapeutic nucleic acids as a whole is relevant.

The state of the prior art and the predictability or unpredictability of the art: At the time of filing, the relevant art considered delivery of therapeutic nucleic acid, as a whole, to be extremely unpredictable. Efficacious, predictable modes of delivery that would provide efficient delivery of the nucleic acid to the target cells had not been developed. Regarding the specific delivery of therapeutic viruses to targeted cells, **Verma et al.,** (1997) states that delivery is the "Achilles heel", and indicates, "[t]he use of viruses is powerful technique, because many of them have evolved a specific machinery to deliver DNA to cells. However, humans have an immune system to fight off the virus, and our attempts to deliver genes in viral vectors have been confronted by these host responses" (pg. 293, col. 3, parag. 1). **Chamber** et al., (1995) previously attributed the greater survival benefit for glioma-bearing mice

treated with a $\gamma_1$34.5 mutant in which the 34.5 gene is interrupted by a stop codon (R4009) rather than by deletion (R3616) due to the low level of stop codon suppression in R4009 allowing for enough viral replication so as to effectively destroy tumor cells, yet not multiply to a level where it can cause encephalitis and taught that the "key to the development of effective oncolytic viruses may well depend on precise control of the expression of the $\gamma_1$34.5 gene" and that "this observation may be exploited to construct still more effective viruses" (page 1415, left column). **Crystal** (1995) has previously recited that "human are not simply large mice. There have been several surprise examples, in which predictions from gene transfer studies in experimental animals have not been borne out in human safety and efficacy trials" (page 409, bottom, left column). Thus indicating that the animal models, by themselves, are not adequate models for therapeutic nucleic acids. Therefore, without an art recognized nexus between the results obtained in animal models and the results which the skilled artisan would reasonably expect to see in humans, the results of applicants animal model data are difficult or impossible to interpret.

Furthermore, and specifically regarding the use of nude mice as human cancer models, Trisha **Gura** teaches in her article titled "Systems for identifying new drugs are often faulty" (Science, 1997; 278:1041-1042),

> "Pharmaceutical companies often test drug candidates in animals carrying transplanted human tumors, a model called a xenograft. But not only have very few of the drugs that showed anticancer activity in xenografts made it into the clinic, a recent study conducted at the National Cancer Institute (NCI) also suggests that the xenograft models miss effective drugs. The animals apparently do not handle the drugs exactly the way the human body does." (See p. 1041, first column)

Gura also teaches, "xenografts tumors don't behave like naturally occurring tumors in humans—they don't spread to other tissues for example. Thus, drugs tested in the xenografts appeared effective, but worked poorly in humans." (See p. 1041, column 2).

Furthermore, **Kerbel** teaches (see "What is the optimal rodent model for anti-tumor drug therapy?" Cancer and Metastasis Reviews Vol. 17:301-304; 1999), "A recurring problem with the use of present models of transplantable tumors is that they frequently respond to anti-cancer drugs or other therapies which then show no activity in humans." (See p. 301, first column). Kerbel indicates a number of specific problems with the mouse model, including (i) concentrations of drugs are used at the maximum tolerated doses for mice, not humans—it turns out that the maximum tolerated dose for mice is often significantly greater than it is for man (see p.301, first column); (ii) most transplanted tumors are very fast growing—drugs are often designed to target rapidly dividing cells; however, natural human tumors often grow much slower. Therefore, the transplanted tumors can show an "exaggerated" response to a drug (see p. 301, second column); and (iii) the response to therapy of a single 'primary' growing transplanted tumor mass is usually what is evaluated rather than that of distant metastases. Regarding (iii), Kerbel teaches, "Clearly this is not representative of most clinical treatment situations in which distant metastases are the target of systemic therapy, and not the primary tumor, which is generally dealt with using surgery." (See p. 302, column 1).

Additionally, the claims encompass treating any type of tumor by any route of administration that results in one or more tumor cells infected with the HSV, however, this does not limit the route of administration to direct delivery to the tumor. Rather the claims still encompass any route of administration. Therefore, the claims encompass treating CNS tumors, such as glioblastomas, by administering the HSV intravenously, subcutaneously, etc. Clearly systemic administration of the HSV (such as by intramuscular, intravenous, or subtaneous administration) would have no efficacy against glioblastoma, wherein the blood-brain barrier

restricts entry of 120nm HSV particles into the brain (**Muldoon** et al. Am. Journ. Pathol. 147(6):1840-1851, 1995).

The above references acknowledge the usefulness of therapeutic nucleic acids for the treatment of cancer and other diseases in the future, however, they also illustrate that there are numerous obstacles that the specification would need to overcome.

The breadth of the claims and the amount of direction or guidance presented in the specification and the presence or absence of working examples:

As such, the disclosed claims are very broad and read on killing any type of tumor by delivering the attenuated HSV by any route to an individual. Clearly, systemic administration of an attenuated oncolytic herpesvirus by intramuscular injection will have little or no efficacy against a glioblastoma, wherein the blood brain barrier restricts entry into the brain of 120 nm HSV particles (**Muldoon** et al., 1995). Furthermore, there is a lack of reference between the in vivo nude mouse model data presented by applicants and results which skilled artisan would expect in humans. That is, there is no example or guidance in the specification that would indicate or guide the skilled practitioner on modifying the treatment of the nude mouse to a human that has a functional immune system. Without guidance from the specification or the prior art, empirical experimentation would be required to determine an effective amount to treat glioblastoma, prostate adenocarcinoma and hepatoma in the individual.

The quantity of experimentation: To attempt to practice the claimed invention in humans, one of skill in the art would turn to the specification for guidance in practicing the invention. As set forth above, however, the specification lacks sufficient guidance to surmount the technical difficulties recognized in the art. Another source of guidance for one skilled in the

art, the prior art (as indicated above), also lacks solutions to overcome the considerable list of obstacles recognized in the field. In the absence of working examples from the specification and the prior art, one of skilled in the art would resort to trial and error experimentation to navigate the obstacles to practicing the claimed invention. Again, as established above, solutions to these technical problems have been elusive despite an enormous amount of experimentation due to a number of factors, including the unpredictable nature of the art. Such unpredictability would warrant even more experimentation, with no true expectation of a measure of success. The amount of experimentation required to practice the claimed invention embodiments would necessitate undue experimentation on the part of one skilled in the art.

In conclusion, given the nature of the invention, the state of the art, the lack of predictability found in the art, the breadth of the claims, the amount of guidance set forth in the specification, and the working example set forth it is concluded that the amount of experimentation necessary to practice the full scope of the claims is very high and is in fact undue.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various

claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 1-14 and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Advani (1997; Int. Journ. Oncol. Rad. Biol. Phys) in view of Carroll et al. (Ann. Surg. 1996); or alternatively Advani (Feb. 1998; Gene Therapy) in view of Carroll et al. (Ann. Surg. 1996) for the reasons of record (see the Office Action mailed on 6/15/2004), which are reiterated below for convenience.

The instant claims are drawn to a method for reducing tumor mass by administering an attenuated HSV to a subject having cancer wherein the HSV genome has been modified in an inverted repeat region such that the HSV has only one active gamma(1)34.5 gene, wherein the HSV is administered in an amount effective to reduce tumor mass. It is noted that the claims explicitly encompass administering HSV R7020, and the claims explicitly encompass administering the HSV to CNS tumors.

Advani (1997) is an abstract that clearly teaches "Human U-87MG glioma cells were grown in the hind limb of athymic mice... and infected with... [HSV] R7020... the tumors were harvested... 14 days after viral injection." Furthermore, Advani teaches, "Herein we demonstrate radiation enhanced viral replication as one of the interactive effects of combining IR and attenuated HSV in treating glioma xenografts and a potential therapeutic motif in the treatment of gliomas." (emphasis added). Therefore, Advani (1997) clearly anticipates the

instant claims as they encompass a method for reducing tumor mass comprising direct delivery of the attenuated HSV to the tumor.

Similarly, Advani (1998) also teaches the same data with more detail, as it is a complete journal article rather than an abstract. Advani (1998) teaches a number of different experiments wherein HSV R3616 is directly administered to human glioma xenografts in nude mice by itself, and in combination with other agents (e.g., see Fig.1, Fig. 2). The injected tumors were allowed to grow and then there volume was measured at different time points (Figs 1 and 2). Avani specifically teaches, "the experiment was repeated with R7020, another genetically engineered attenuated virus" (see p. 161, bottom of second column), indicating that the R7020 was also injected into glioma xenografts in a nude mouse model and tumor volume was measured at certain time points.

Neither Advani (1997) or Advani (1998) explicitly teach the teach that the attenuated HSV virus could be used to treat a non-CNS tumor in vivo.

Carroll teaches treatment of non-CNS tumor using an attenuated HSV (hrR3). Specifically, Carroll teaches a method for treating colon carcinoma liver metastasis by administering an attenuated HSV directly to the tumor (e.g., see abstract).

Therefore, it would he been prima facie obvious at the time of invention that the method taught by Advani (1997) or Advani (1998) would have also been able to treat a non-CNS tumor such as a colon carcinoma liver metastasis in an animal or human, with a reasonable expectation of success. One of ordinary skill in the art would have been motivated to modify the method Advani (either 1997 or 1998) to treat a non-CNS cancer because Carroll teaches that attenuated HSVs can be used to treat non-CNS-type tumors. Furthermore, the in vitro findings that taught

by the Advani references are indicative of an expectation of success for directly administering the vectors to tumors in vivo.

Response to Arguments

Applicant's arguments filed 11/28/2005 have been fully considered.

With respect to the rejection of claims 1-4 and 15 under 35 USC 112, 2nd paragraph for being indefinite for encompassing "non-natural protein" (claim 15) is now moot in view of the cancellation of claim 15.

With respect to the rejection of claims 1-4 and 15 under 35 USC 112, 1st paragraph for insufficient written description of the genus of "non-natural proteins" encompassed by the claims (claim 15) is now moot in view of the cancellation of claim 15.

With respect to the objection to the specification and the rejection of claims under 35 USC 112, 1st paragraph for comprising new matter, Applicants first argue that the amendment to change the number of non-essential genes from 47 to 46 is to correct a typographical error that would have been obvious to one of skill in the art upon consideration of the cited Roizman reference is not persuasive. Applicants argue that the Roizman reference discloses 46 genes nonessential HSV genes. However, upon close examination of the Roizman reference, it does not appear that Roizman teaches 46 non-essential HSV genes. In fact, looking at Table 1 as well

as page 11310, first column (see first full paragraph) Roizman teaches, "The 45 accessory ORFs specify, which are not required for viral replication in cells in culture..." Thus, Roizman does not appear to disclose 46 non-essential HSV genes, but rather 45 non-essential genes. It is respectfully pointed out that the Applicants have not indicated where in the reference Roizman explicitly discloses 46 non-essential genes. Should Applicants disagree they are asked to indicate where support for 46 non-essential genes can be found in the Roizman reference. With respect to the amendment entering the names of the 46 non-essential genes, Applicants contend that the asserted new matter is merely the names of the 46 non-essential HSV genes and argue that the names of the genes is not an attempt to add essential subject matter by incorporation from a non-patent publication because the names of the genes were known in the art (as evidence by the Roizman reference).. This is not found persuasive because the names of the genes is considered essential material.

In response, Applicants are respectfully reminded that MPEP § 608.01(p) indicates:

> "An application as filed must be complete in itself in order to comply with 35 U.S.C. 112. Material nevertheless may be incorporated by reference, *Ex parte Schwarze*, 151 USPQ 426 (Bd. Ape. 1966). An application for a patent when filed may incorporate 'essential material' by reference to (1) a U.S. patent, (2) a U.S. patent application publication, or (3) a pending U.S. application, subject to the conditions set forth below. 'Essential material' is defined as that which is necessary to (1) describe the claimed invention, (2) provide an enabling disclosure of the claimed invention, or (3) describe the best mode (35 U.S.C. 112). In any application which is to issue as a U.S. patent, essential material may not be incorporated by reference to (1) patents or applications published by foreign countries or a regional patent office, **(2) non-patent publications**, (3) a U.S. patent or application which itself incorporates 'essential material' by reference, or (4) a foreign application. Nonessential subject matter may be incorporated by reference to (1) patents or applications published by the United States or foreign countries or regional patent offices, (2) prior filed, commonly owned U.S. applications, or (3) non-patent publications however, aperients and/or other forms of browser executable code cannot be incorporated by reference. See MPEP § 608.01. Nonessential subject matter is subject matter referred to for purposes of indicating the background of the invention or illustrating the state of the art."

It is also respectfully pointed out that MPEP § 1.57 (c) specifically indicates:

> "'Essential material' may be incorporated by reference, but only by way of an incorporation by reference to a U.S. patent or U.S. patent application publication, which patent or patent application publication does not itself incorporate such essential material by reference. "Essential material" is material that is necessary to:
>
> (1) Provide a written description of the claimed invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and set forth the best mode contemplated by the inventor of carrying out the invention as required by the first paragraph of 35 U.S.C. 112..."

In the instant case, the names of the non-essential genes are considered "essential material" because it is necessary to describe the claimed invention. Since the new material added to the specification is "essential material" it may not be incorporated by reference to a non-patent publication as indicated above (See MPEP § 608.01(p)). Therefore, the new material is new matter. Furthermore, since claim 5 explicitly recites the genes which are considered new matter, the rejection is appropriate and the rejection is not withdrawn.

With respect to the rejection of claims 1-14 and16 under 35 USC 112, 1st paragraph for not being fully enabled, Applicants arguments have been fully considered but are not persuasive.

Applicants first contend that the claims do not encompass gene therapy but rather viral therapy for tumors and request that the examination focus on the merits of the claimed subject matter.

In response, it is acknowledged that the instant claims are drawn to viral therapy of tumors. However, viral therapy of tumors does require that the therapeutic nucleic acid (virus)

be delivered specifically to the desired cells, in this case the tumor cells. As such, an evaluation of delivery of the therapeutic nucleic acids as a whole is relevant. The rejection has been adjusted to more clearly indicate why the claimed methods are not fully enabled and do not focus on gene therapy.

Applicants also contend that the use of an oncolytic virus (such as HSV) to kill cells was not unfamiliar to those of skill in the art. In response, it is acknowledged that the use oncolytic viruses was known in the prior art (e.g., see the Advani references of record). However, considering the breadth of the claims (e.g., treating any type of tumor by any route of administration) in view of the teachings of the prior art (e.g., see the teaching of Muldoon as indicated above) does indicate that the claimed invention is not enabled to the full breadth encompassed by the claims.

With respect to the state of the prior art, Applicants argue that the instant claims are not methods of gene therapy and that the challenges of gene therapy are reduces or eliminated from the claimed methods of viral therapy. This is not persuasive because the issues with respect to the specificity of delivery of the therapeutic nucleic acid, as a whole, are relevant to the instant claims.

With respect to the Verma reference, Applicants argue that the generalized comments of Verma et al. (1997) relating to challenges in using any virus as a vector in gene therapy are not informative as to whether the immune system presents a challenge to using modified HSV as tumor therapeutics because knowledge in the art specific to HSV reveals that one of skill knew that HSV could function in an immunocompetent host. In response, this is not persuasive because Verma does speak generally to the administration of therapeutic viral vectors (which

includes oncolytic HSV vectors). Furthermore, Applicants have not presented any evidence which indicates that the HSV vectors when administered systemically would not be recognized by the hosts' immune response.

With respect to the Chambers reference, Applicants request clarification of the Examiner's position. In response, Chambers was cited as a relevant prior reference because it demonstrates that further experimentation is required with respect to the use of HSV vectors for the treatment of tumors.

With respect to the Advani reference, it is acknowledged that the instant claims are not explicitly drawn to curing cancer. As such, the Advani reference has been removed from the rejection.

With respect to the Crystal reference, Crystal indicates that the animal models, by themselves, are not adequate models for therapeutic nucleic acids. Therefore, without an art recognized nexus between the results obtained in animal models and the results which the skilled artisan would reasonably expect to see in humans, the results of applicants animal model data are difficult or impossible to interpret.

Applicants argue that the reliance on the Gura reference is misplaced because the issues of Gura are not central issues to the predictability of the art. The Examiner respectfully disagrees. Gura teaches that the results found in nude mice are not necessarily representative of the results that will be found in other animals including humans. This speaks directly to the predictability of the claimed invention.

Applicants also argue that the reliance on the Kerbel reference is also misplaced. The Applicants argue that non of the enumerated problems is informative on the of the state of the art

and does not affect the capacity of the xenograft model to predict behavior in a non-xenograft model. In response, The Examiner respectfully disagrees. Kerbel does teach specific issues that demonstrate that the xenograft animal model is not necessarily predictive of the outcome in non-xenograft models.

Applicants also argue that the route of administration is not essential. This is not persuasive because the art explicitly teaches that the route of administration is critical. Applicants also argue that one of skill in the art would recognize administration routes would not allow the virus to gain access to a particular tumor and would not use such a route; rather, they would use an administration route that provides access to the tumor.

In response, it is acknowledged that the level of skill in the art required to make and use the claimed invention is high. However, the claims encompass any route of administration wherein one or more tumor cells are infected with the HSV. It is noted that claims 6 and 8 explicitly indicated that the cancer is a noncentral nervous system cancer and claims 7 and 9 explicitly indicate that the cancer is a central nervous system cancer. Therefore, the claims encompass treating central nervous system cancers as well as non-central nervous system cancers by any administration that results in infection of tumor cells. Since the claims encompass treating the tumors by any route of administration, the claims not enabled for the full scope for the reasons of record, as indicated above. It is respectfully pointed out that the only route of administration taught by the specification which would result in the infection of tumor cells (in view of the unpredictable nature of the invention) is directly administering the HSV to the tumor

by direct injection into the tumor (e.g., see Example 3, page 9, first paragraph), which is indicated as the scope the claims which is enabled. Furthermore, Applicants appear to be arguing that since the claims encompass embodiments which are enabled, one of skill in the art would recognize which embodiments are enabled and use the route(s) of administration that are enabled by the specification. However, since the claims clearly encompass embodiments which are not enabled by the specification, the rejection is appropriate. It is also respectfully pointed out that amending the claims such that the are limited to enabled embodiments would overcome the instant rejection. As indicated above, the limitation that the route of administration is one that results in one or more tumor cells being infected with the HSV does not limit the claim to direct administration of the HSV to the tumor. Therefore, applicant's arguments are not persuasive and the rejection is not withdrawn.

With respect to the rejection of claims under 35 USC 102 Applicants argue

In response, it is respectfully pointed out that the specification does not appear to define the term "patient" as human or in any way that excludes mice. Since Advani clearly teaches treating mice which are suffering from cancer, the mice are patients. Furthermore, it is pointed out that the specification explicitly discloses treating mice having tumors and there are no examples disclosing the treatment of human patients. Therefore, Applicants arguments are not persuasive and the rejection is not withdrawn.

With respect to the rejection of claims under 35 USC 103, Applicants argue that the claims have been amended such that they are now limited to treating a "patient". Furthermore,

Applicants contend that because a "patient" is understood in the art as being a person (i.e., human) and since the cited references do not contemplate treating a human or suggest or provide motivation to treat a person, the rejection has failed to set forth a *prima facie* case of obviousness.

In response, it is respectfully pointed out that the specification does not appear to define the term "patient" as human or in any way that excludes mice. Since Advani clearly teaches treating mice which are suffering from cancer, the mice are patients. Furthermore, it is pointed out that the specification explicitly discloses treating mice having tumors and there are no examples disclosing the treatment of human patients. Additionally, it appears that Applicants are arguing against the references individually. In response, to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Therefore, Applicants arguments are not persuasive and the rejection is not withdrawn.

Applicant's arguments, with respect to the rejection(s) of claim(s) under 102 and 103 have been fully considered and are persuasive with respect the previous rejections. However, upon further consideration, a new ground(s) of rejection is made for the reasons indicated herein.

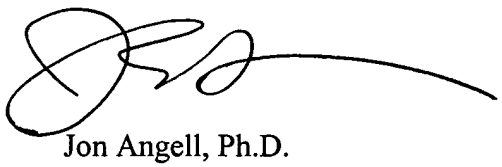
Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon Eric Angell whose telephone number is 571-272-0756. The examiner can normally be reached on Mon-Fri, with every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Jon Angell, Ph.D.
AU 1635